Advancing Transfusion and Cellular Therapies Worldwide

ASSOCIATION BULLETIN

#06-07

Date: November 3, 2006
To: AABB Members
From: D. Michael Strong, PhD, MT(ASCP), BCLD(ABB) – President
Karen Shoos Lipton, JD – Chief Executive Officer
Re: Transfusion-Related Acute Lung Injury

Summary
This bulletin updates information contained in Association Bulletin #05-09 and contains additional recommendations to further reduce the risk of transfusion-related acute lung injury (TRALI) in blood and blood component recipients. This bulletin does not change the requirements relating to AABB Standard 5.4.2.1.

Recently, the AABB Board of Directors convened the AABB TRALI Working Group (Working Group) and charged it with 1) exploring the effects on blood safety and availability of potential intervention strategies to reduce the incidence of TRALI and 2) reporting or recommending to the Board any guidance or communication to the membership. The Working Group recommended and the Board adopted the following recommendations to reduce the incidence of TRALI.

1. Blood collecting facilities should implement interventions to minimize the preparation of high plasma-volume components from donors known to be leukocyte-alloimmunized or at increased risk of leukocyte alloimmunization.
2. Blood transfusion facilities should work towards implementing appropriate evidence-based hemotherapy practices in order to minimize unnecessary transfusion.
3. Blood collection and transfusion facilities should monitor the incidence of reported TRALI and TRALI-related mortality.

AABB recommends that blood collection and transfusion facilities begin implementation of these TRALI risk reduction measures for all high plasma-volume components as soon as possible according to the following schedule.

1. Complete full implementation of the measures relating to plasma components and whole blood by November 2007.

2. Complete full implementation of the measures relating to platelet components as soon as possible, but in any event no later than November 2008.

No specific interventions (other than working towards implementing evidence-based hemotherapy practices) are recommended at this time for lower plasma-volume components, because the per-unit risk attributed to antibody-mediated TRALI from these components has been documented to be significantly lower.

Background

Pulmonary reactions, which include dyspnea of unknown etiology, transfusion-associated circulatory overload and TRALI are still among the most frequent adverse consequences of blood transfusion; the contribution that each of these syndromes makes to posttransfusion pulmonary complications is unknown.[1] Although much about TRALI is still not completely understood, a significant advance has occurred with the standardization of the definition of TRALI, as set forth by a National Heart, Lung, and Blood Institute working group and the Canadian TRALI Consensus Conference Panel. Both of these definitions are based solely on clinical and radiological parameters.[2,3] Despite the relatively straightforward criteria, the diagnosis of TRALI is still problematic in some cases because of the difficulty in ruling out left atrial hypertension and/or acute lung injury (ALI) resulting from other causes when other risk factors for ALI are present in a transfused patient.

Information about the frequency of TRALI-related deaths was provided in Association Bulletin #05-09. Since the publication of that bulletin, new data have been accumulated. TRALI was the most frequent cause of transfusion-related death reported to the Food and Drug Administration (FDA) between October 2003 through September 2005. [Personal communication, Dr. Leslie Holness, FDA.] An average of 24 such deaths were reported annually from 2003-2005. Assuming that there are 5.3 million transfusion recipients per year, and that all transfusion-related fatalities are reported to FDA, it can be estimated that TRALI contributes to mortality in at least 1 in 220,000 transfusion recipients.[4] Assuming under-reporting to FDA and using literature estimates (a TRALI incidence of 1 in 5000 transfused components, a fatality rate of 5%, and the annual transfusion of 22 million components*), TRALI can be counted as a contributing factor in approximately 220 deaths each year.[4,5] Additionally, recent data from two studies conducted in specific patient settings (one in multiple intensive care units and one throughout a tertiary care hospital), suggest that the incidence of fatal and nonfatal TRALI is 1 in 1300 to 1 in 2400 components transfused, once cases with other ALI risk factors are excluded, and 1 in 370 to 1 in 1000 components transfused if such cases are included.[6,7]

Substantial circumstantial evidence exists that many cases of TRALI are caused by transfusion of components containing antibodies to leukocytes. Animal and ex-vivo models of TRALI support this etiology and, in the clinical setting, many recipients who develop TRALI have received a donor unit with antibodies directed against an antigen present on the recipient's leukocytes. Such antibodies may be directed against HLA Class I or Class II antigens, or non-HLA neutrophil antigens (HNA antigens). Because donors with HLA and/or HNA antibodies are likely to be highly alloimmunized, it is also

possible that such donors may have other types of antibodies that have not been identified, and that these antibodies could be the cause of TRALI in some cases.[8]

*This figure represents an estimation of components transfused in the United States (US) in 2004; the number given in the 2005 nationwide survey has been adjusted by dividing the number of apheresis platelet equivalents by six to estimate the actual number of apheresis units transfused.

Data from a small number of look-back studies performed on previous recipients of components from donors implicated in TRALI cases indicate that recipients transfused with components containing specific HNA antibodies appear to develop pulmonary symptoms more frequently than recipients transfused with HLA antibodies from similarly implicated donors.[9-11] There is also evidence suggesting that recipient antibodies to donor leukocytes cells might be implicated in some TRALI cases, but this association has been reported less frequently.

In some TRALI cases, no antibody is detected in either the donor or the recipient. There is evidence that some of these cases are caused by nonantibody substances contained in stored blood (ie, biological response modifiers such as lipids that activate neutrophils).[12] Although the relative incidence of TRALI caused by antibodies vs biological response modifiers is unknown, a review of data concerning the biological response modifier mechanism indicates that the largest series of cases caused by this mechanism is characterized by less severe complications (less frequent ventilator support and lower mortality rate) than previously described cases attributed to the antibody mechanism.[13,14]

The highest frequency of leukocyte antibodies is found in female donors who have previously been pregnant. The prevalence of antibody increases with the number of pregnancies, from a small percentage in women who report no pregnancy history, to approximately 25% after three or more pregnancies.[15] Overall, about 15 to 20% of female donors have HLA antibodies compared with an estimate of <1% of male donors (who presumably acquired their antibody from alloimmunization to leukocyte antigens following previous transfusions). The frequency of HNA antibodies in donors has not been well studied but limited data indicate that this frequency is very low, even in previously pregnant women.[16]

Several years ago, investigators from the United Kingdom (UK) Serious Hazards of Transfusion (SHOT) system determined that the rate of TRALI occurrence was five- to sevenfold greater for blood components that contained high volumes of plasma [eg, Fresh Frozen Plasma (FFP) and buffy-coat-derived platelets resuspended in plasma from one of the donors in the pool] than for lower plasma-volume components [eg, additive solution Red Blood Cells (RBCs) and Cryoprecipitated AHF]. These data also showed that the majority of TRALI cases resulting from transfusion of these two types of components involved a leukocyte antibody-positive female donor. On the basis of the SHOT analysis, the UK adopted a policy to minimize the transfusion of FFP and buffy-coat-derived platelets from female donors.[17] Since the implementation of this policy in October 2003, the number of cases of TRALI arising from these components has decreased substantially.[18] However, because case definitions and ascertainment procedures in the

UK may be different than in the US, it is not clear how well these data predict the outcome that would be achieved if similar procedures were to be implemented in the US.

In 2004, the Canadian TRALI Consensus Conference Panel stated that blood collection agencies in a given jurisdiction should evaluate whether interventions to reduce TRALI risk would have a projected benefit in excess of any potential adverse impact, such as a decrease in the availability of needed blood components.[2] Recently, the American Red Cross (Red Cross) has analyzed cases of fatal TRALI reported to its organization.[19] From 2003 to 2005, 550 reports of suspected TRALI (including 72 fatalities) were reported to the Red Cross. All fatalities were reviewed and classified by three physicians as either "probable TRALI" or of "unrelated etiology," with independent review of the associated serologic investigation. The number of reports increased each year and the rate varied by geographic region. Retrospective review of fatalities revealed 38 cases of probable TRALI, the majority of which (24 of 38) followed plasma transfusion. A female leukocyte antibody-positive donor was involved in 75% of cases (18 of 24) involving plasma transfusion and in 60% of cases (three of five) involving apheresis platelets. Female antibody-positive donors were more likely to be associated with probable TRALI than with cases of unrelated etiology [p=0.0001; odds ratio = 9.5; 95% confidence interval (CI) = 2.9-31.1]. The rate of probable TRALI among recipient fatalities was higher for plasma components (1:202,673; odds ratio = 12.5; 95% CI = 5.4-28.9) and apheresis platelets (1:320,572; odds ratio = 7.9; 95% CI = 2.5-24.8) than for red cells (1:2,527,437). Male donors contributed 64.5% and 52.0% of distributed apheresis platelets and plasma components, respectively, in 2005. The analysis concluded that plasma was responsible for the majority of probable TRALI fatalities in the Red Cross system and that as many as six fatalities per year (or 47% of all TRALI fatalities) were linked to plasma from female donors with leukocyte antibodies.

Based on the current state of knowledge, it is evident that no single intervention can prevent all cases of TRALI. However, current data about the incidence and severity of antibody-mediated TRALI in the US suggest that precautionary risk reduction strategies should be implemented at this time. Although it is not possible to quantitate what the effect of a risk reduction strategy will be on overall TRALI incidence, the data are highly suggestive that targeted risk reduction strategies could reduce the number of cases of severe TRALI.

Recommendations

TRALI has been shown to be associated with the transfusion of blood components containing HLA or HNA antibodies. The reduction of the transfusion of blood components containing these antibodies should substantially reduce the incidence of TRALI. Therefore, in order to increase patient safety the following steps should be taken:

1. Blood collecting facilities should implement interventions to minimize the preparation of high plasma-volume components from donors known to be leukocyte-alloimmunized or at increased risk of leukocyte alloimmunization.

2. Blood transfusion facilities should work towards implementing appropriate evidence-based hemotherapy practices in order to minimize unnecessary transfusion.
3. Blood collection and transfusion facilities should monitor the incidence of reported TRALI and TRALI-related mortality.

For purposes of these recommendations, high plasma-volume components include the following:

- FFP obtained from whole blood
- FFP obtained from apheresis [plasmapheresis, concurrent (combined) red cell-plasmapheresis, concurrent (combined) platelet-plasmapheresis]
- Plasma Frozen Within 24 Hours After Phlebotomy (FP-24) obtained from whole blood or apheresis
- Plasma, Cryoprecipitate Reduced (ie, cryo-poor plasma) obtained from whole blood or apheresis
- Apheresis platelets
- Buffy-coat-derived platelets resuspended in plasma from one of the donors in the pool
- Whole blood

AABB recommends that blood collection and transfusion facilities begin implementation of these TRALI risk reduction measures for all high plasma-volume components as soon as possible according to the following schedule.

1. Complete full implementation of the measures relating to plasma components and whole blood by November 2007.
2. Complete full implementation of the measures relating to platelet components as soon as possible, but in any event no later than November 2008.

Other than working towards implementing evidence-based hemotherapy practices, no specific interventions are recommended at this time for lower plasma-volume components, because the per-unit risk attributed to antibody-mediated TRALI from these components appears to be significantly lower. Lower plasma-volume components include:

- Red Blood Cells
- Platelets prepared from whole blood
- Cryoprecipitated AHF

Approaches to Meeting the Intent of the Recommendations

The approach to implementing these recommendations will necessarily differ among facilities because of logistics, the effect of the measures on component availability, and component mix within a particular facility.

Considerations for Blood Transfusion Services

In response to the new understanding of the TRALI risk of high plasma-volume components, transfusion services should work with clinicians to educate them about these TRALI risks and about the need to work towards implementing evidence-based hemotherapy practices of all blood components, with special emphasis on high plasma-volume components. Recent randomized clinical trials in critically ill patients provide evidence for a causal relationship between the number of RBC units transfused and the development of ALI and also suggest that restrictive transfusion practice may be an effective way to reduce the incidence of TRALI.[20,21]

Other studies have clearly shown that RBCs, platelets, and FFP are still used excessively in clinical settings such as the intensive care unit, that active interventions are required to decrease inappropriate utilization, and that decreasing inappropriate utilization will decrease adverse transfusion reactions.[22,23]

Transfusion services should follow up on all cases of reported TRALI and work with their blood suppliers to perform a proper case investigation. Transfusion services are essential participants in monitoring the effectiveness of TRALI risk reduction strategies through their careful investigation and reporting of suspected TRALI reactions.

The basic elements of TRALI case investigations are described in Association Bulletin #05-09.[24] Further recommendations about TRALI case investigations will be provided in a future association bulletin.

Considerations for Blood Collection Facilities

The potential approaches to meeting the intent of the first recommendation (minimizing preparation of high plasma-volume components from donors known to be leukocyte-alloimmunized or at increased risk of leukocyte alloimmunization) include the following steps:

1. Preparing high plasma-volume components intended for transfusion from male donors. In the case of recovered plasma from whole blood donations, plasma derived from female donors would be used preferentially for further manufacture.

   The feasibility of the approach of using male donors to supply plasma products intended for transfusion can be assessed based on national transfusion statistics. Since more than 7 million of the whole blood units collected in the US are from males, and only 4 million units of plasma are transfused, there appears to be a large excess capacity to provide male plasma. However, due to a less than ample supply of some blood groups, achieving a plasma supply exclusively from males for AB and B plasma may be difficult for some collection organizations.

   Logistical considerations are also important. Transport of units of whole blood from the collection site to the processing laboratory within the eight hour time limit currently imposed on the production of FFP may further complicate the implementation of some of the TRALI risk reduction measures suggested. This latter problem can be solved by producing less fresh frozen plasma and more plasma frozen within 24 hours. Factor VIII is the only factor significantly affected by a delay in the time to freezing with one study showing a decrease of activity (from time zero) of 16% at eight hours and 36% at 24 hours.[25] Thus, 84% of Factor VIII activity is available in FFP (frozen within eight hours) and 64% in plasma frozen within 24 hours; other studies have corroborated these findings.[26] Many situations requiring plasma transfusion (ie, reversal of warfarin effect) involve patients with elevated levels of Factor VIII. The clinically necessary level of Factor VIII in vivo is approximately 30% and in situations where Factor VIII is low, the indicated therapy is either Factor VIII concentrate or cryoprecipitate.

2. If eliminating the preparation of high plasma-volume components from female donors is not possible without compromising component availability, the use of high plasma-volume components from female donors could be continued if those donors are selected in such a way as to minimize the likelihood of their having been alloimmunized and having developed leukocyte antibodies. This could be accomplished by

    a. obtaining a pregnancy history from female donors and using plasma from those women who give a history of never having been pregnant
    b. performing leukocyte antibody testing on female donors who donate a particular type of product (ie, Apheresis Platelets)
    c. a combination of both of these approaches

    Institutions using the Donor Health History Questionnaire that wish to obtain a pregnancy history as part of their TRALI risk reduction strategy would need to add such a question to the space designated for additional questions.

    With regard to leukocyte antibody testing, adoption of this approach would require deciding whether both anti-HLA and anti-HNA testing would be performed, as well as selecting the particular assay(s) to be used; this decision may be influenced by the current limited availability of anti-HNA testing in the US. For female donors of childbearing potential, a policy would be needed to address if and when antibody testing would be repeated.

    Approaches that eliminate the use of female donors with leukocyte antibody are likely to diminish the availability of apheresis platelets by 7 to 10%. Thus, blood collection facilities will need to replace these lost components. Possible approaches to accomplish this include increased recruitment of male apheresis donors, increasing the number of apheresis platelet components obtained from current male apheresis donors, or supplying some of their platelet inventory as whole blood derived platelets.

3. A further step toward restricting the use of leukocyte antibody-positive donors could involve obtaining a lifetime transfusion history from all donors (both males and females) and either excluding donors with such a history from high plasma-volume component production or testing such donors further for leukocyte antibodies. It is estimated that about 4 to 5% of donors have been transfused, but the prevalence of leukocyte antibodies in this group is not well established. At present, it is unclear how much additional safety would be obtained from including this step in a TRALI risk reduction program.

    Because different mechanisms may contribute to TRALI and because the current understanding of TRALI pathophysiology is incomplete, no set of interventions is available that will eliminate the risk of TRALI. However, it should be possible to

substantially decrease the incidence and mortality from TRALI provided that appropriate interventions are fully implemented.

Making a meaningful impact on the incidence of TRALI may require some significant operational changes in collection, manufacturing, and/or screening strategies. However, as has been observed in the UK, these changes should be realizable in a relatively short period.

Other Potential Strategies for TRALI Risk Reduction

Two additional strategies could be considered to decrease the amount of plasma transfused from high-risk, high plasma-volume components. One of these strategies is the use of pooled solvent/detergent-treated (SD) plasma in place of single-donor plasma. Although there are no definitive peer-reviewed published data on this issue, reports from countries that transfuse a specific commercial SD plasma product indicate that this product does not appear to cause TRALI.[27] Other factors would, of course, also enter into the decision whether to transfuse SD plasma or single-donor plasma. An FDA-licensed SD plasma product is not currently available in the US.

A second strategy is to store platelets (apheresis or whole-blood-derived) in platelet additive storage solutions. No platelet additive storage solutions are currently licensed in the US, although some are available in other countries. These solutions permit a reduction of approximately two-thirds in the volume of plasma transfused with platelets. No data exist that evaluate whether reduction of this amount of plasma volume will have an impact on the incidence of antibody-mediated TRALI.[28]

Monitoring the Effectiveness of Interventions

Facilities should monitor the incidence of reported TRALI (using the Canadian TRALI Consensus Conference Panel definition), as well as TRALI-related mortality before and after implementation of their TRALI risk reduction programs. This monitoring is necessary to obtain data for an assessment of the effectiveness of the interventions, as well as to determine the residual risk of TRALI.

Implementation Support

The AABB Board of Directors recognizes that implementation of these interventions will be a challenging enterprise. AABB is committed to providing ongoing support, in the form of educational and informational materials, for the implementation of these strategies. Questions can be submitted to AABB via email (technical@aabb.org).

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